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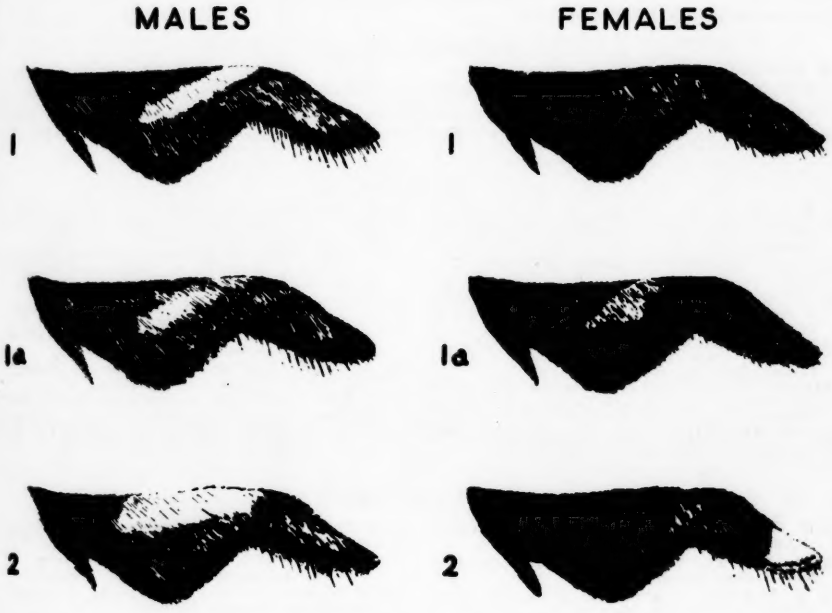

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Genetics and Cybernetics

"Lens Rupture" in the Mouse

A New Alkaptonuria Pedigree

Chromosome Inversion in the Tomato

"Somatic Meiosis" by Cold Treatment

VOLUME 41 JANUARY, 1950 NUMBER 1

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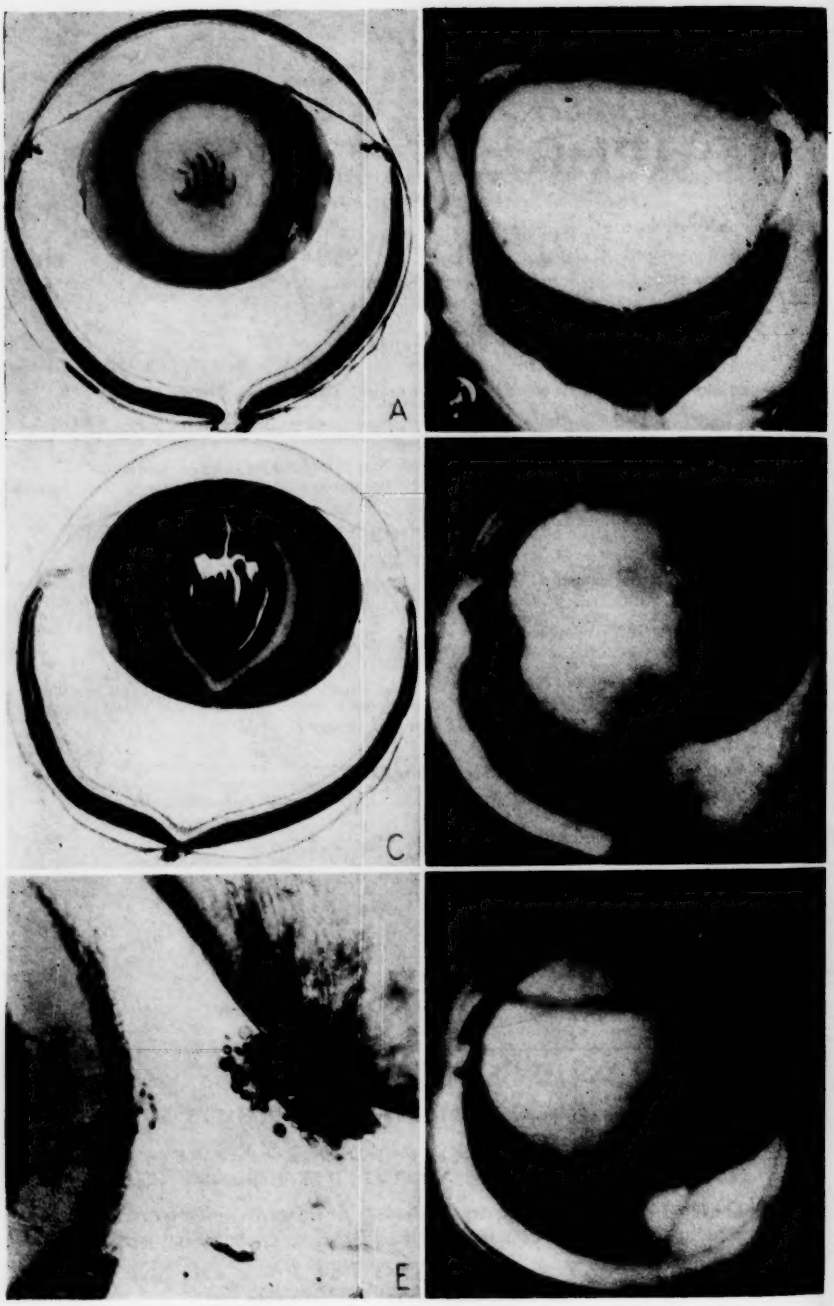


NORMAL AND "LENS RUPTURE" EYES

Figure 1

A and *B* show the normal mouse eye at four weeks and 17 days respectively. *C* and *D* show lens rupture (*lrlr*) eye at 14 and 18 days respectively. *E* and *F* show *lrlr* eyes at 20 days; *E* shows the posterior pole of lens with extrusion beginning. *F*—Early rupture appears as a flocculent haze below the lens. See text, Page 4, for further details.

THE INHERITANCE AND EXPRESSION OF THE "LENS RUPTURE" GENE

In the House Mouse

F. CLARKE FRASER AND M. L. HERER*
McGill University

THIS paper describes the genetic behavior and expression of the recessive mutant "lens rupture" recently identified in this laboratory by the authors.[10] The condition involves a cataractous degeneration of the lens with expulsion of the lens nucleus posteriorly through the ruptured lens capsule. Its relation to other cataractous conditions reported in the literature will be considered after the present condition has been described.

Genetic Data

Because of the variable time of onset of the "lens rupture" condition, all mice included in the following data were classified as to the presence of lens rupture at the age of three months or more. This is well past the maximum age at which the onset of the "lens rupture" condition has been observed.

a. *Recessive nature*

Breeding tests have established that the condition is inherited as a simple recessive factor. 74 offspring of crosses between affected animals and normal ones from unrelated strains remained phenotypically normal throughout life (Table I, cross 1). In 286 F_2 animals from such crosses there were 66 "lens rupture" animals, a close approximation to the expected value of 71.5 for a 1:3 segregation (Table I, cross 5). Of 307 offspring from heterozygous animals backcrossed to "lens rupture" homozygotes there were 144 "lens rupture" progeny. The deviation from a 1:1 segregation is not significant (Table I, cross 6).

b. *Penetrance*

The gene, in the homozygous state, shows complete penetrance on its present genetic background. In generations F_3 to F_8 in two homozygous "lens rupture" strains observed over the past eighteen months, a total of 108 animals, classified at the age of three months, all had bilateral cataract. However, there are indications that on other genetic backgrounds the penetrance may be appreciably reduced. Further evidence is being collected on this point.

c. *Linkage tests*

In the crosses suitable for detecting a partial sex-linkage of the "lens rupture" gene, no consistent deviation from equality was found in the distribution of mutant animals between the sexes. In the F_2 generation from a cross where the mutant gene was introduced by the female grandparent, no significant excess of *lrlr* females were obtained (Table I, cross 3). Similarly, no significant excess of *lrlr* males occurred in the F_2 of the reciprocal cross (Table I, cross 4). There is, therefore, no reason to suspect a partial sex-linkage of the *lr* gene.

The following loci have been found to segregate independently of the "lens rupture" gene: albino (*c*), flexed tail (*f*), waved-2 (*wa-2*) and shaker-2 (*sh-2*). Results are summarized in Table II.

Morphological Observations

The development of the condition has been observed from three viewpoints: (1) *in vivo* with the aid of a dissecting microscope—by this method the albino eye could be observed clearly through the transparent iris; in the non-albino eye observations were made following dilatation of the pupil with atropine, (2) *gross dissections*, in which the eye, following fixation in Bouin's picro-formol, was cut open with a razor blade and examined under a dissecting microscope, and (3) *histological sections* prepared from eyes embedded in celloidin, and stained with hematoxylin and eosin. The following description will try to synthesize these three approaches into a coherent picture. To keep the terminology comparable to that of ophthalmology we will refer to the region of the optic pit as "posterior"

*The authors wish to acknowledge their indebtedness to Dr. J. V. V. Nicholls of the Department of Ophthalmology, Royal Victoria Hospital, Montreal, who provided several histological preparations, one of which is illustrated in Figure 1*E*, and gave us much valuable advice during the preparation of this manuscript. The senior author is deeply grateful also to Professor P. M. Bayne and the Biology Department, Acadia University, Wolfville, N. S., for providing laboratory facilities during part of this work, and to the National Research Council of Canada for its financial aid.

although it is realized that in the mouse, "proximal" would be a more accurate term.

At about two to three weeks of age the first outwardly visible sign of the abnormality can be seen as a small, milky-white spot deep in the interior of the eyeball. Histological examination at this stage shows a subcapsular aggregation of eosinophilic homogeneous droplets at the posterior pole of the lens (Figure 1*C*). As the substance increases in quantity the gap at the posterior suture widens as if the tips of the fibres were being forced away from those on the other side of the suture line. Their displacement causes a distortion of the capsule which can be seen in gross dissections as a small raised ring at the posterior pole (Figure 1*D*), and *in vivo* as a thin refractile ring-like line deep in the eyeball. The space encircled by the ring may be clear or may contain minute refractile globules, flakes or rods.

As the process continues, lens substance is extruded into the vitreous chamber. This is seen in dissections (Figure 1*F*) as a white puff of flocculent material in the cone formed by the branches of the hyaloid artery as they spread out over the posterior surface of the lens. The hyaloid artery is normally present in the first three post-natal weeks—(Figure 1*B*). Figure 1 *E* shows the corresponding histological preparation, in which lens material is seen emerging through the defective lens capsule.

During these early stages the nuclear material of the lens moves toward the posterior pole (Figure 1*C*), and eventually can be seen, both histologically and *in vivo*, protruding through the posterior lens capsule (Figure 2*A*) at which stage the distorted capsule may tear quite extensively (Figure 2*B*).

As it is expelled, the nucleus becomes opaque so that it appears *in vivo* as a dense well-defined, ivory-colored mass on which the Y-shaped suture-line is often visible. Variable amounts of cortical material can be seen as a cloudy, milky-white, flocculent precipitate in the vitreous chamber, and sometimes in the angle that the iris makes with the cornea.

From this stage on, the course of events is quite variable. The process may halt here indefinitely (Figure 2*A*), or the nucleus may be completely extruded into the vitreous chamber and become wedged between the lens and the retina (Figure 2*C*, *D*), or occasionally pass into the anterior chamber and come to rest between the iris and the cornea.

Numerous vacuoles that develop in the shrunken lens, especially in the equatorial region (Figure 2*C*), can be seen as hyaline droplets with refractive outlines, giving the equator of the lens a "scalloped" appearance. Internally, the lens may develop irregular, cloudy, milky-white opacities, or may remain hyaline. In a majority of cases it tears away from the suspensory ligaments and becomes displaced to varying degrees. At six to seven weeks of age, in eighteen percent of the eyes observed, the soft degenerate lens has passed through the pupil and is situated in the anterior chamber (Figure 2*E*, *F*), or lies part way through the pupil, with the iris constricting it into a dumb-bell shape.

The incidence of lens in the anterior chamber (Table III) was significantly higher in males (51.7 percent) than in females (9.3 percent, $P < 0.01$). The incidence of bilateral occurrence (9.7 percent) was higher than that expected if distribution of the condition was random (3.3 percent), but the excess was not statistically significant ($P = 0.07$). Right eyes were more often affected than left eyes, but not significantly so ($P = .3$-$.5$).

In the later stages of the condition there occurs a folding of the retina into a raised ring around the optic nerve head (Figure 2*E*, *F*). This is not accompanied by degenerate changes in the retinal cells, but is not thought to be an artefact since it does not occur in young *lrlr*

TABLE I Segregation of *lr* in various types of cross.

	lr		*lr*+				
Cross	♂	♀	♂	♀	T	X^{2*}	P*
1. *lrlr* × *lr* + *lr* +	0	0	38	36	74		
2. *lrlr* × *lrlr*	52	56	0	0	108		
3. F_2 of *lrlr* ♀ × *lr* + *lr* + ♂	23	26	83	85	217	0.763	0.8-0.9
4. F_2 of *lr* + *lr* + ♀ × *lrlr* ♂	8	9	22	30	69	0.121	0.98-0.99
5. F_2, Total	31	35	105	115	286	0.574	0.8-0.9
6. B.C. *lrlr* + × *lrlr*	73	71	79	84	307	1.326	0.7-0.8

*On the expectation of simple recessive segregation.

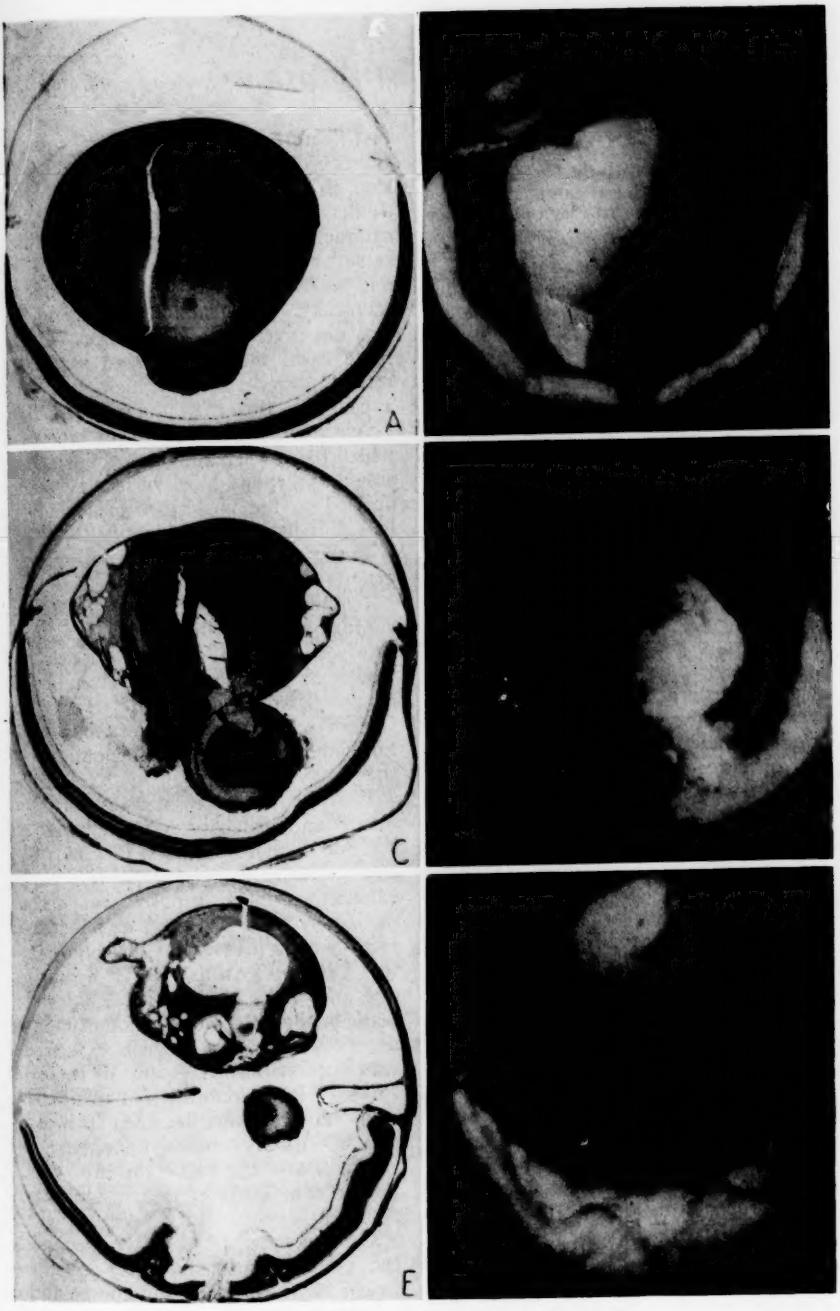
TABLE III Distribution of eyes with lens in the anterior chamber in 72 adult "lens rupture" mice.

Lens in anterior chamber in	♂	♀	T
Left eye	3	1	4
Right eye	7	1	8
Both eyes	5	2	7
Neither eye	14	39	53
	29	43	72

TABLE II. Segregation of *lr* and various other mutant loci "m" in linkage tests.

Cross	Phenotype	*LrM*	*Lrm*	*lrM*	*lrm*	T	X^{2*}	P*
1. F_2 of *lrlr*; *cc* × *LrLr*; *CC*		125	32	33	12	202	2.709	0.3-0.5
2. BC (*lrlr*; *cc* × *LrLr*; *CC*) × *lrlr*; *cc*		30	20	31	33	114	3.544	0.3-0.5
3. F_2 of *lrlr*; *ff* × *LrLr*; *FF*		24	7	8	3	42	0.159	0.98-0.99
4. BC (*lrlr*; *ff* × *LrLr*; *FF*) × *lrlr*; *ff*		33	39	26	34	132	2.606	0.3-0.5
5. F_2 of *lrlr*; *Wa-2Wa-2* × *LrLr*; *wa-2wa-2*		103	32	34	7	176	1.677	0.5-0.7
6. F_2 of *lrlr*; *8h-28h-2* × *LrLr*; *sh-2sh-2*		106	28	30	12	176	1.617	0.5-0.7

*On the expectation of independent assortment.



LATER DEVELOPMENT OF LENS RUPTURE

Figure 2

All six photographs show *lrlr* eyes at various stages of development. *A*—eye at five months, showing "posterior lenticonus." *B*—eye at five weeks, showing rupture of the lens capsule. *C* and *D*—eye at five weeks and eleven weeks respectively. In both *C* and *D* the nucleus is extruded. *E* and *F*—eyes at four weeks and eleven weeks respectively. In both specimens the lens is in the anterior chamber.

eyes or normal eyes of any age. The detachment of the retina from the sclera, on the other hand, is considered artifactual, since there is no evidence of the subretinal fluid that one would expect to see in pathological separation.

Subsequent happenings are confined largely to minor reparative changes. Adhesions may form where the lens or nucleus lies in contact with a source of fibroblasts (optic pit or iris). In those pigmented eyes that have the nucleus in the anterior chamber, invasion of the nucleus by pigmented tissues can be observed *in vivo*. Sometimes "reduplication" of the iris occurs, presumably by a folding back of the free edge of the iris and the formation of adhesions (Figure 2*E*). Occasionally the cornea undergoes vascular infiltration and becomes opaque. Otherwise the situation remains relatively stable until death of the animal.

No attempts have been made to estimate the effect of the condition on vision beyond the observation of an active pupillary light reflex in adult "lens rupture" animals.

Discussion

The "lens rupture" mutant* constitutes a case where a change at a single genetic locus is associated with a series of events each of which by itself is a recognized ophthalmological entity. The lenticular opacities constitute "cataract." The stage at which the nucleus is distorting the capsule at the posterior pole of the lens constitutes a "posterior lenticonus." Finally there is an "ectopia" (atypical position) of the lens with varying degrees of irideal displacement. It is possible to obtain virtually unlimited material at all stages of this process and to observe each stage by a variety of methods. Such an unusually favorable medium for study should be of interest ophthalmologically as well as genetically.

We did not find any cases in the literature on hereditary cataract in man[17] and other mammals[3] which could be identified positively with the "lens rupture" condition. Bourne and Gruneberg[3] report a recessively inherited cataract in the rat in which the external appearance described resembles that seen in *lrlr* eyes, and they illustrate a section in which the appearance of the lens resembles that of an *lrlr* lens just before rupture of the capsule. Cohrs[5] describes a cataractous condition in the mouse which Gruneberg[12] thinks may be comparable to the rat cataract described above, and in which capsular rupture is demonstrated in the one cataractous animal observed microscopically. The genetics of the condition was not investigated. However in both these cases there is also an associated retinal degeneration, which does not appear in the *lrlr* mutant. Rochon-Duvigneaud[15] describes a mole eye in which there was rupture of the lens capsule and a round block of lens substance applied to the posterior surface of the lens, but he does not identify this block with the nucleus or mention any relevant genetic data.

Nothing indicative of a lenticular rupture was described in the hereditary cataract found in mice by Koch and Gowen,[14] in the recessively-inherited congenital cataract of cattle reported by Gregory *et al.*[11] or the cataractous condition inherited as a simple dominant in the rat.[16]

Ehrlich[9] reviews eight cases of rupture of the lenticular capsule in humans. All but one of these occurred in eyes which had previously been observed to be cataractous. The rupture was accompanied by pain, swelling, and increased intra-ocular pressure (glaucoma) and was followed in some cases[13] by shrinkage and dislocation of the lens, which occasionally came to lie in the pupil or anterior chamber. A genetic influence was not established in any of these instances. It is doubtful if a relationship could be established between such cases, which usually follow long-standing cataract, and the "lens rupture" condition in which nuclear expulsion occurs at an early stage of the process.

On the other hand it seems possible that some relationship may exist between "lens rupture" and the condition of "posterior lenticonus," a bulge on the posterior surface of the lens, in which

*"It is probable that the hereditary cataract described by Smelser, G. K. and L. Von Sallman, *American Journal of Ophthalmology* 32: 1703-1713, 1949, is identical with the 'lens-rupture' mutant.

there may be tearing of the lens capsule, posterior displacement of the nucleus, and opacities at the posterior pole and in the nucleus.[6, 7, 1]

The *lrlr* lens, which ordinarily passes through this stage, occasionally remains in such a condition more or less indefinitely (Figure 2*A*). Perhaps mechanical differences between the two types of lens account for the fact that capsular rupture is usually followed by expulsion of the lens nucleus in mice but not in men.

Dr. Nicholls has pointed out that the degenerative changes observed in the lens correspond to those which follow operative rupture of the capsule in humans. It is, therefore, with the events leading up to capsular rupture that one must begin to study the mode of action of the "lens rupture" gene.

At present it is not entirely clear whether the early degenerative changes in the lens substance follow rupture of the lens capsule, or whether the capsule ruptures because of the stresses brought about by the internal changes. We have never observed capsular lesions without signs of internal degeneration; but we have seen internal changes without being able to find a capsular defect in the same eye; however the possibility remains that a minute capsular lesion might not have been included in the prepared sections.

The number of etiological agents associated with a cataractous degeneration of the lens is so great[4, 2, 8, 1] that it would be impossible to deduce anything about the mode of action of the lens rupture gene by analogy with that of other cataractogenic agents. We must rather turn to physico-chemical experiments and further histological studies on the pre-cataractous *lrlr* lens for some indication of the way in which the gene acts to initiate the series of events described in this paper.

Summary

1. The "lens rupture" gene (*lr*) is a simple recessive factor not linked with sex, albinism, flexed-tail, waved-2 or shaker-2.

2. In the homozygous condition the mutant gene is associated with rupture of the lens capsule, cataractous degeneration of the lens, and expulsion of the lens nucleus with varying amounts of cortical substance into the vitreous chamber. The lens shrinks, tearing the suspensory ligaments, and may pass through the pupil into the anterior chamber.

3. The relationship of "lens rupture" to ophthalmological conditions in humans is discussed.

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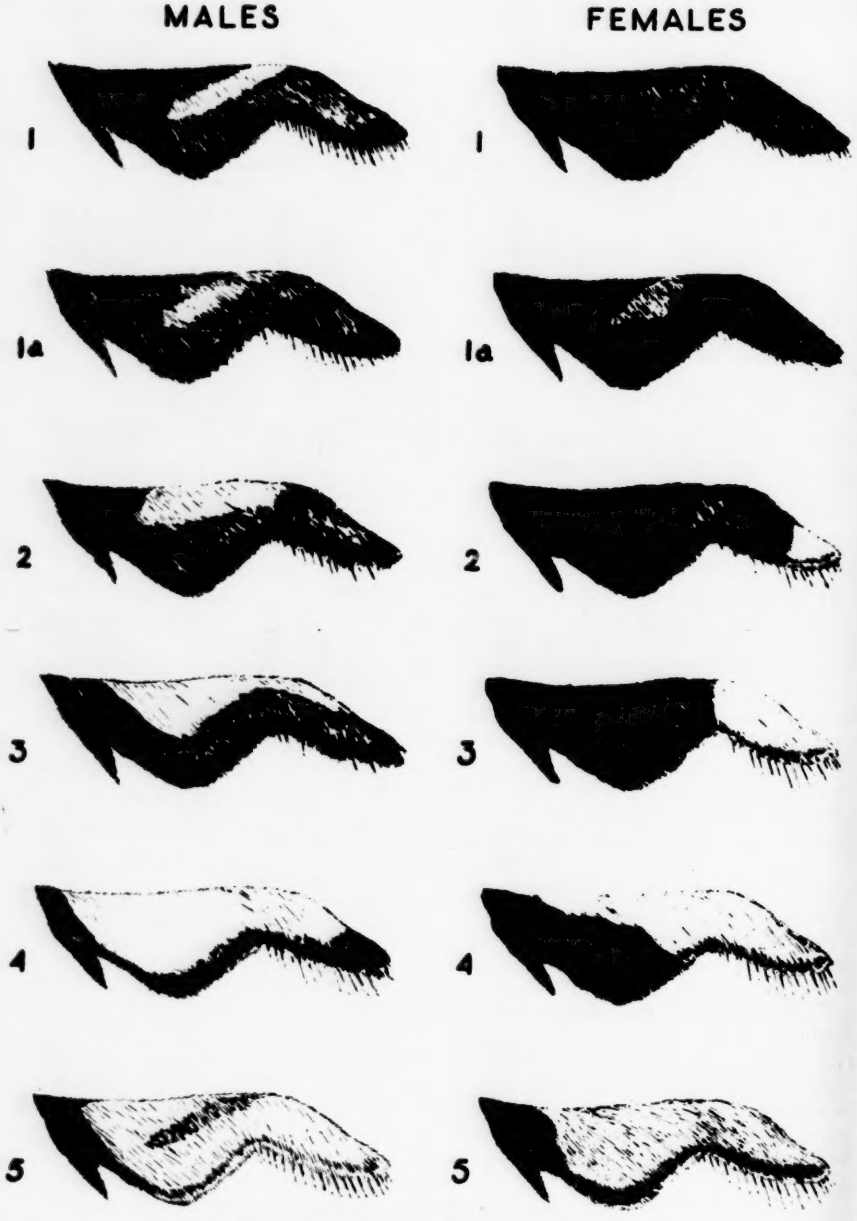

SEX-DIMORPHISM IN DOWN PATTERNS

Figure 3

Down patterns of day-old New Hampshire chicks show variation in sex-dimorphism according to the scheme sketched here. A high correlation was discovered between the down patterns of male chicks and the sex eminence (See Figure 4). Males with grades 4 and 5 had the "more masculine" type of sex eminence.

A RELATIONSHIP BETWEEN THE WING DOWN PATTERN AND SEX EMINENCE

in New Hampshire Chicks*

I. L. Kosin

Washington Agricultural Experiment Station, Pullman

THE existence of sex dimorphism in the wing down pattern of New Hampshire day-old chicks is now an established fact. The work of Jaap[1] and of others has amply demonstrated that the sex of the newly hatched chick of that breed can be identified with a relatively high degree of accuracy on the basis of wing down coloration pattern.

It is possible that in line with the known strain differences in adult plumage coloration similar strain differences may exist in the expression of such economically important phenotypic characteristics. Consequently, a study was undertaken by the author in 1947 to examine and classify the wing down pattern in chicks of the New Hampshire strain maintained at the Poultry Plant of this Station. In the course of the study, nearly 1500 chicks were examined and classified on the basis of wing down pattern and sex predicted accordingly. In each case this was immediately followed by an examination of the sex eminence, to verify the accuracy of sex identification. The chick was then killed and autopsied to provide the final check on that point.

Following the preliminary tests, at least five definite "basic" types of wing down coloration were recognized in the male New Hampshire chicks. Briefly, this classification is based on the extent and position of the yellowish-white down area on the dorsal side of the wing in relation to the "normal" basically reddish-brown down color background. The five classes were arbitrarily identified by numerals from 1 through 5, in a progressive series of increasing amount of light down area over the wing. Type 1, the most easily recognizable male pattern, showed a definite white stripe running diagonally on the dorsal side of the wing cephalad and just proximal to the ulna-radial and humeral articulation. At the other extreme was Type 5 in which the basic reddish-brown down background has been almost completely replaced by the yellowish-white down. See Figure 3.

In the female chicks, which are basically darker in color than the males, the most easily recognizable wing down pattern was considered to be the one in which the entire dorsal side of the wing plane was uniformly reddish-brown. This was designated as Type 1. In females the light colored down was graded on the basis of its progressive proximal extension beginning with the tip of the wing and gradually extending over the metacarpal, carpal and ulna-radial regions and, finally, covering almost the entire wing. Accordingly, Types 2 through 5 were subjectively assigned to this graded series, characterized by the encroachment of light down over the basic dark background. Female Type 5 and male Type 5 were often difficult to distinguish. Fortunately, the chicks belonging to this type were only rarely found among the females examined in the course of this study; the light wing males were much more common. See Figure 3 for the illustration of the male and female basic pattern types.

During the earlier routine trial tests on the accuracy of "sight sexing" by the wing down method, the impression was gained that the wing down pattern and the size and shape of the sex eminence were correlated: the cockerel chicks of

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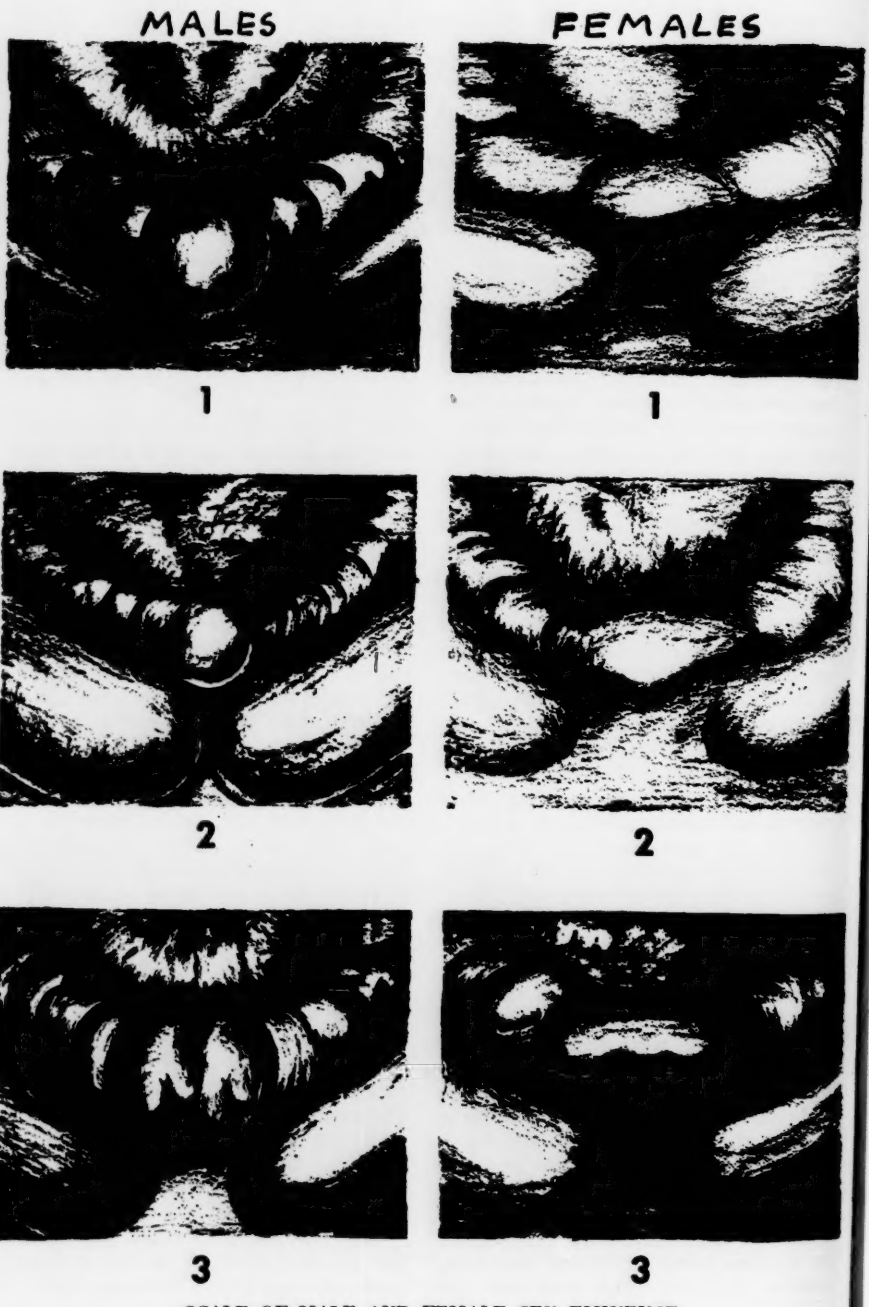

SCALE OF MALE AND FEMALE SEX EMINENCE

Figure 4

The usual method of chick-sexing used in commercial hatcheries is based on the morphology of the sex eminence. In the male chicks, extremely light wings were correlated with the more male types of sex eminence.

Types 3, 4, and 5, i.e. those with the progressively greater extension of the yellowish-white down area, appeared to possess the more "masculine" types of sex eminence. By contrast, the females of Types 1 and 2, i.e. those showing none or only a small light down area, appeared to have either no eminence at all, or only a small structure of indefiinite shape closely approximative to type *h* of Canfield.[1]

These somewhat cursory observations led to a study, the purpose of which was to check more specifically on the apparent relationship between these two morphogenetically divergent structures.

Correlation Between Down Pattern and Sex Eminence

Accordingly, a total of 561 chicks of both sexes hatched at the Station in 1948 over a period of several months were "sexed" both by the wing down and sex eminence methods with each chick being scored on the basis of its wing down pattern and the size and shape of sex eminence. A 10× "Multi-focuser" was used to facilitate the identification and typing of sex eminences. The down coloration was scored according to the schedule of types already described, while the sex eminences were graded according to a modified version of Canfield's[1] classification. Thus, his male Types *a* and *b* were classed as a composite Type 1; *c* became Type 2; *d* and others—composite Type 3. For the purpose of a statistical analysis, these Types were coded to be worth 3, 4, and 5 units respectively.

In the females, Canfield's Type *g* (complete absence of the eminence) became Type 1; *h*, and *i* (progressive increase in the size of the tongue-like eminence) were classed as a composite Type 2; the remaining, as a composite Type 3. The code values of 2, 3, and 4 were assigned to these three types respectively.

This classification of the male and female sex eminence types is illustrated in Figure 4.

The accuracy of the down method of sexing in this last series of observations was 92.3 percent, (as checked by subsequent post mortem examination) which was considered to be satisfactory for the purpose of this study. The distribution of the chicks according to the classification adopted in this investigation is summarized in Table 1.

Errors in sexing by this method were largely caused by calling Type 5 (extremely light) or a variant of Type 1 females (extremely dark with a "ghost"-like stripe pattern) as males. An occasional error was made in mistaking a variant of male Type 1 (dark with a "ghost"-like stripe pattern over the humeral region) for a female.

The average scoring of the chicks according to these two criteria gave the results shown in Table II.

While the standard errors of the class means in the above table are high, the consistency of the trend, particularly striking in the males, cannot be overlooked. A statistical analysis of the male data gave the coefficient of correlation of +0.341 for within-class variation. This value of r is statistically significant at the 1 percent point. In the females, the corresponding correlation was only +0.060.

The apparent existence of a relationship between the "maleness" of the down color on the one hand and of the sex eminence on the other, led to further examination of the day-old male New Hampshire chicks according to these two criteria.

Upon further study it was found that the first three types of the wing down classification could be broken down into two fairly clear-cut groups, A and B, based on the degree of distinctness in the basic pattern (group A) as contrasted to the more indistinct basic pattern in group B.

A check of 103 male chicks (sex checked subsequently by post mortem examination) classified into these two groups showed that, on the whole, the group A pattern was associated with a larger and/or a more distinctly male type of sex eminence. The B group pattern, on the other hand, was associated with a "less male" type of eminence. The mean unit value of the sex eminence of the chicks in group A was found to be 4.4 while in the B group chicks the mean value was 3.5. The application of chi-square test for goodness of fit to these data produced a chi-square value of 0.0962, thus corroborating the original observation of the existing association between the two characteristics in the male chick.

Discussion

The existence of a highly significant positive correlation between the wing down pattern and size of the sex eminence in day-old W.S.C. strain New

TABLE I. Frequency distribution of wing down pattern types in New Hampshire chicks.

Males		Females	
Class	*Per cent*	*Class*	*Percent*
1	41.2	1 and 2 combined	69.3
2	22.0		
3	14.7	3, 4 and 5 combined	30.7
4	14.7		
5	7.4		

TABLE II. Relationship between wing down pattern and sex eminence type in New Hampshire chicks.

Males		Females	
Wing down class	*Coded size of sex eminence*	*Wing down class*	*Coded size of sex eminence*
1	3.8±0.16	1	2.1
2	3.9±0.60	2 through 5	2.8
3	4.1±0.28		
4	4.4±0.24		
5	4.6±0.46		

Hampshire chicks gives rise to several theoretical considerations. The apparent association of two characteristics so different in their morphological expression and morphogenetic history may, at first glance, be surprising. However, the fact that similar close associations among unrelated quantitative, qualitative and behavioral characteristics exist in other animal material[2, 8, 5, 6] make it easier to accept and speculate about the nature of the association observed in the present study.

Pleiotropy should not be overlooked as a possible explanation of the association, although there is no direct evidence pointing in that direction. It is possible that one gene or one and the same set of genes is primarily concerned with controlling the outward expression of these two sex dimorphic characteristics. As MacArthur[8] has stated, the pleiotropic action of a gene may become manifested in a variety of ways. He singled out one of the hormonal-pathways as likely to be a more common avenue by means of which such unifying genic action may be accomplished. The existence of such genic-endocrine relationship has been demonstrated in chickens by Munro[9] *et al.* and it offers an attractive explanation for the observations recorded in this study. It is known that the size of the sex eminence in the male chick is at least in part hormonally controlled[7]. Furthermore, the phenotypic expression of chromatophore cells also is partly controlled by hormones[3, 10]. Is it not possible then, that the gene or genes which determine the wing down pattern in New Hampshires may also influence the activity of the pituitary gland, thus affecting, indirectly, the embryonic development of the sex eminence? Although the capacity of an embryonal chick gonad to secrete sex hormones may be open to question, so far there has been no conclusive evidence to the contrary.

Our present knowledge of the genetics of down coloration in New Hampshire chicks is extremely meager. The subject is obviously complex, involving the question of time action of genes. Otherwise it would be difficult to account for the striking differences between the chick down and the adult feather color patterns. Of the color genes in New Hampshires, the recessive sex linked gene for "gold" ground color is the only one known at present that may account for sex dimorphism in down coloration. However, at best its action can only be that of a "trigger" gene acting together with other, at present unidentified, complementary genes or genes in an allelomorphic series, to produce the characteristic male and female wing down pattern. It should be interesting to repeat the approach used in this investigation with Barred Plymouth Rocks where at least two sex-linked genes (*B* and *S*) are known to be concerned with the down pattern. Perhaps the strikingly different head spot patterns in the male and female chicks of that breed could be used as one of the criteria.

Summary

Observations based on 561 New Hampshire chicks showed that in the male chicks there is a positive and a highly significant correlation between the "maleness" of the wing down pattern and of the sex eminence. Furthermore, the more distinct is the down pattern in the male chick, the "more male" is the sex eminence in appearance. In the females these associations were lacking.

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SEGREGATION AND REDUCTION IN SOMATIC TISSUES

IV. Reductional Groupings induced in *Allium cepa* by low temperature

C. Leonard Huskins and K. C. Cheng*

In previous papers of this series it has been shown that sodium nucleate treatments result in an appreciable proportion of the divisions in root tip meristems being converted into a reductional type of mitosis. Cold treatment has been assumed to affect the nucleic acid cycle of the chromosomes[1,9] and it has now been found that a result similar to that of sodium nucleate is produced in the onion and some other plants by keeping them at a temperature of 5°-6°C. In neither case, however, is it yet established that it is really a changed nucleic acid content or cycle that produces the effects. A quantitative analysis of the onion data will be presented by Dr. K. Patau and K. C. Cheng. Herein the reduction process will be illustrated and interpreted tentatively in the light of the data available from both low temperature and sodium nucleate treatments, since they appear to be similar yet jointly different from the effects of a number of other treatments.

In control roots of these and other experiments it has surprisingly been found that from 1-2 percent of all mitoses may be of the reductional type, though only a few of them produce reduced nuclei. Huskins and Steinitz found haploid cells in *Rhoeo* and *Allium* and recently Vaarama[8] has shown that meristems of colchicine-induced tetraploid *Ribes nigrum* ($2n = 32$) have chromosome numbers ranging from 4 to 32. Following Upcott he assumes that the cause of reduction is a separation of the chromosomes onto the two halves of a split spindle. Our evidence indicates that with both sodium nucleate and cold treatment, separation of the chromosomes into two groups begins in prophase and that formation of twin spindles is a later factor in the production of nuclei with reduced chromosome number.

The production of two or more chromosome groups under the influence of chemical treatments has been noted, or illustrated without being remarked upon, by numerous workers since Nemec in 1904 worked with chloral hydrate. Most workers have, however, been concerned with the increase of chromosome number by chemical and other treatments and have ignored the reduction problem.

Materials and Methods

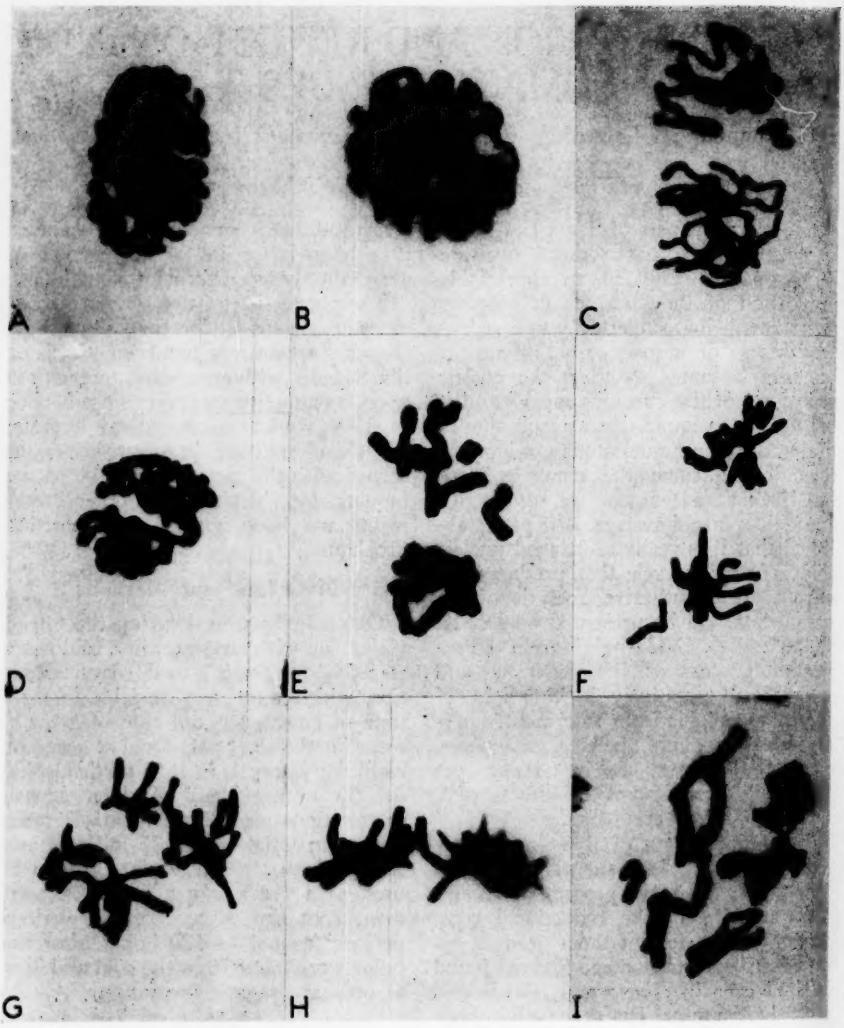
Onion bulbs were kept on the top of vials filled with tap water in a cold room at 5-6°C for from 5 to 64 days. Root tips, which were very variable in their time of emergence and rate of growth, were for the most part fixed at seven or eight day intervals in 1 : 3 acetic alcohol for 30 minutes and Feulgen squash preparations made from them. Paraffin section material cut at 25 microns and stained with Crystal Violet-Iodine was used as a check. In a second experiment root tips were fixed at various periods from 4 to 120 hours after the bulbs were taken from the cold and kept at ordinary room temperatures.

Results

Cold treatment increases the proportion of reduction-type divisions ("reductional groupings") from the 1-2 per-percent found in the present controls and other untreated materials to more than 5 percent. This high percentage continues for about a day after removal from the cold.

Separation of the chromosomes into

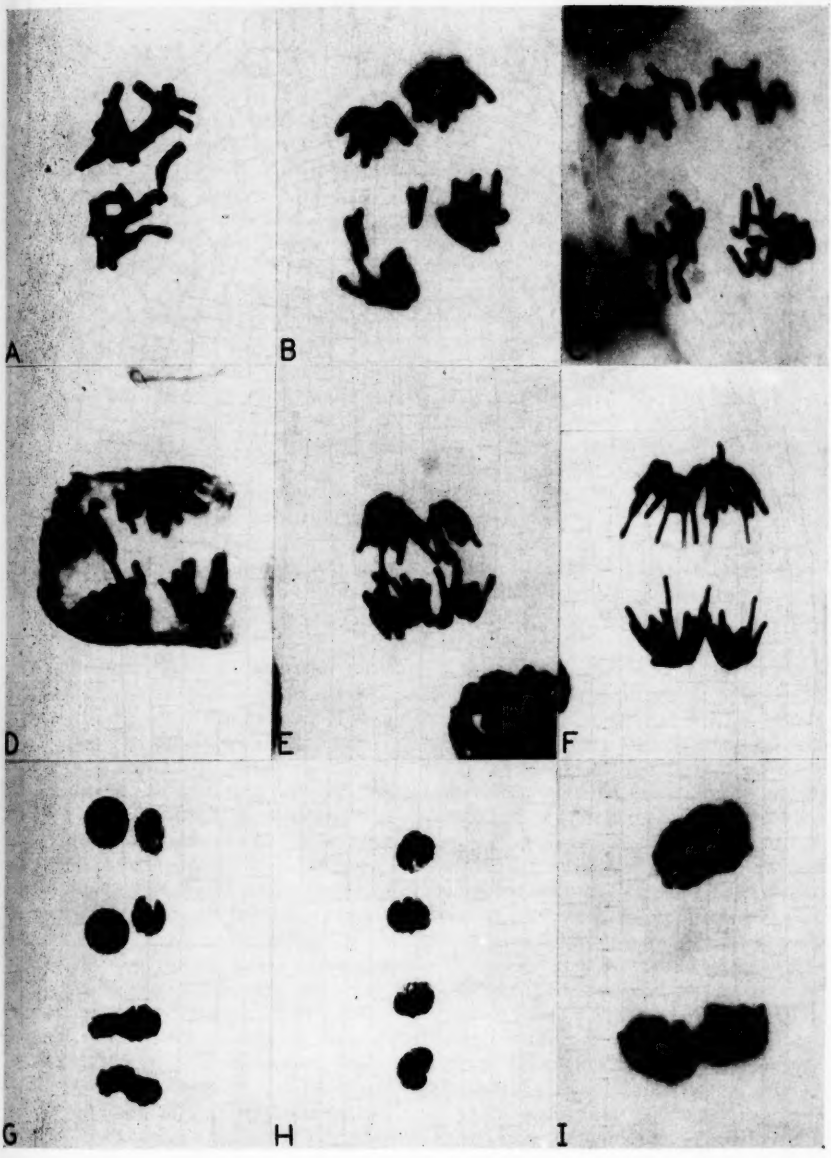
*Professor and Research Assistant respectively, Department of Botany, University of Wisconsin. The Program in Cytology is supported in part by grants from the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.



LOW TEMPERATURE INDUCED "SOMATIC REDUCTION"

Figure 5

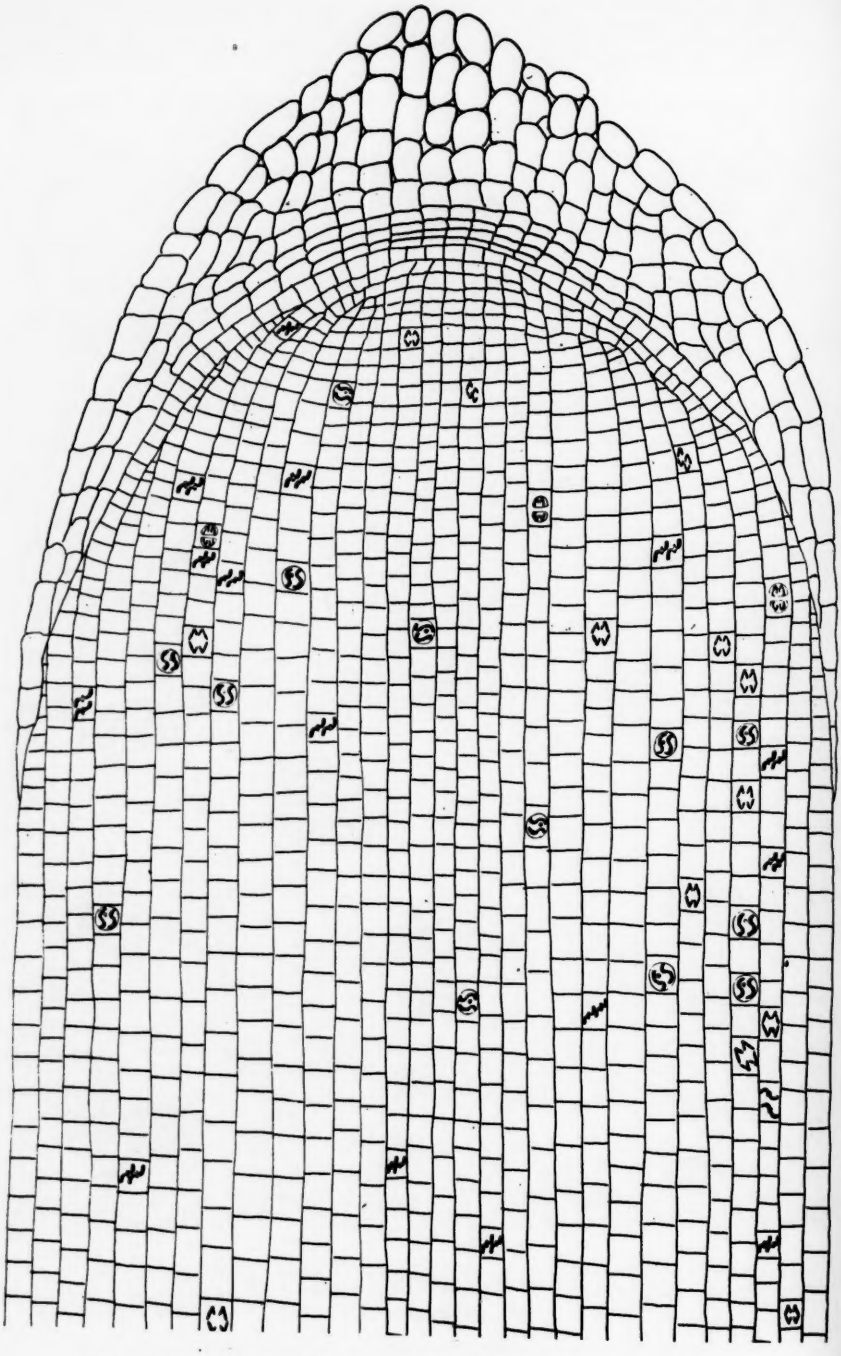
Cold treatment doubles or triples the frequency of reductional groupings of chromosomes found occasionally in normal root tips. These photographs of typical preparations illustrating this phenomenon show the variation in the degree of separation of the groups, and the extent of anaphase separation. See text for details. *A, C, D, E, F, G, I,* 1125×; *B, H,* 1170×.



STAGES FOLLOWING REDUCTION

Figure 6

Division figures following reductional groupings of chromosomes induced in onion by low temperatures. See text for details. *A, C, D, E*, 1125×; *B, F*, 1170×; *G, H*, 565×.



LOCATION AND ORIENTATION OF REDUCTIONAL DIVISIONS

Figure 7

Composite diagram of a sectioned onion root tip showing all the types of reductional groupings it contained and the orientation of plates and spindles. See text for further details.

two groups is apparent at prophase stages, as shown in Figure 5 *A, B* and *C*, and these appear to be much more frequent than groupings at later stages of mitosis. At later prophase and metaphase stages the two groups may lie farther apart as in Figure 5 *D, E, F,* or they may remain so close together that it is difficult to decide whether or not to regard them as definite groupings. Similarly, when they begin to go into anaphase they may be as separate as in Figure 5 *G* and *H* or relatively little separated as in 5 *I* and 6 *A*.

Correlatively the two anaphase-telophase groupings may be as separate as in Figure 6 *B, C* and *D* or appear as "double anaphases" Figure 6 *E* and *F*. The four nuclei resulting from this division may be arranged quadrilaterally as in Figure 6 *G* or linearly as in Figure 6 *H*. Sometimes two separate nuclei are formed at one end of the cell and a single fused nucleus at the other, Figure 6 *I*.

The orientations of all the reductional metaphase and anaphase plates and of their spindles which were found in a single root, sectioned at 25 microns, are shown in a composite diagram, Figure 7. A single chromosome or pair of daughter chromosomes represents a reduced group, regardless of the number of chromosomes it contains.

The impression gained from studies of reductional groupings following either sodium nucleate or cold treatment of several different plants is that there is a great preponderance of equal or nearly equal distributions over all other groupings excepting in *Rhoeo* which is an interchange heterozygote. However, selective survival is probably involved, the "expected" distribution is not necessarily binomial and there is a very large subjective factor involved in direct determinations. Patau and Steinitz[6] show how bias in such statistics can be greatly reduced. Dr. Patau has also developed a method employing length measurements which should eliminate systematic bias in the determination of whether segregation or only numerical reduction is involved. This work is still in progress but has clearly rendered statistically highly significant proof of more than random segregation of homologues in the somatic reductions of *Rhoeo*. The differences between the chromosomes comprising the haploid set of *Allium cepa* are insufficient to enable direct determination of whether or not the separation of the groups involves more than random segregation of homologues, as Wilson and Cheng[7,10] found in *Trillium* treated with sodium nucleate.

Discussion

There are many resemblances between the reductional groupings induced by cold or sodium nucleate on the one hand and a range of chemicals, chloral hydrate, ethylene glycol, inorganic phosphates, colchicine and other alkaloids, etc. on the other. There appear, however, to be significant differences and this problem is being given extended analysis.

Obviously, nuclei with reduced chromosome numbers can result from various treatments and it is clear, despite the fact that they have been so generally overlooked, that they also arise spontaneously with an appreciable frequency. Even if separation were random with respect to homologues, a proportion of the reduced nuclei would contain a normal haploid complement and these, at least, would be expected to give rise in some instances to haploid cells and tissues. If the original organism is a polyploid, the reduced tissues may be expected in some cases to produce either vegetative or sexual offspring with the ancestral chromosome number, as suggested in the initial paper of this series,[3] in which a number of cases that previously had no explanation were cited. Recently, Vaarama[8] has established it in *Ribes*. From the evolutionary point of view there is now no doubt that polyploidy is reversible; the problem is to find means of inducing reduction (or segregation followed immediately by doubling) with a frequency that might provide a useful tool for the plant breeder.

The production of a cell containing one diploid and two haploid nuclei, as in Figure 6 *I*, provides a possible mechanism whereby, through subsequent nuclear fusion, a triploid cell can arise from a diploid. The discovery by M. B. Crane[2] of a triploid shoot on a grafted and decapitated diploid tomato is therefore no longer inexplicable. Conversely, the occurrence of only tetraploid offspring from this triploid when, after being sterile through two years of vegetative propagation, it produced two fruits may have been due to a somatic change to tetraploidy in one branch. One of our associates, L. Chouinard,[4] has recently obtained triploid and diploid roots and a diploid shoot from tetraploid *Rhoeo discolor* and a number of cases of 12:6 somatic reductions in the triploid.

Summary

A reductional type of mitosis which occurs in root tips can be greatly increased in frequency in cells of *Allium cepa* by growing the bulbs at low temperatures.

Addendum

Since the foregoing article was submitted for publication, Levan and Lotfy, *Hereditas* 35: 337-374, 1949, have cited similarities between the effects of sodium nucleate and of other chemicals, especially colchicine, and suggested alternatives to Huskins'[3] interpretations. As indicated in the above and other articles, unpublished data furnish a background to some of the interpretations (see [5] which should appear shortly) but it did not seem appropriate to withhold all data and possible interpretations until the results were, by our standards, conclusive. Similarities were stressed by our associate, Dr. M. Kodani, in a paper published coincidently with that in which Huskins stressed the apparent differences between effects of sodium nucleate and those of colchicine—as far as the latter had until then been recorded (or stressed) by other workers. It may help clarify the situation to emphasize that: a) our controls show that we are analyzing a process that also occurs spontaneously, though rarely; b) spindle formation *follows* reductional grouping and some previous workers have therefore been inverting cause and effect in their interpretations; c) preliminary comparisons of sodium nucleate and colchicine effects by Wilson, Allen, and Powell (in press) indicate significant differences, but even if the initial effects had proved to be the same, the end results would be quite different—since colchicine inhibits the spindle the chromosome *number* (following chromatid separation) would (as Levan and Lotfy point out) not be reduced, whereas following sodium nucleate or cold-induced or spontaneous reductional grouping, spindle action may continue and reduction in chromosome number; as well as segregation, may therefore occur. With Levan and Lotfy's final conclusion that "systematical observations on a standardized method are needed . . ." we are in full accord:—such were initiated three years ago and are progressing steadily, but as they say: "This work is . . . often tedious."

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A CYBERNETICAL ASPECT OF GENETICS

H. KALMUS*

IT is now widely realized, and if in some quarters still contested, that the similarities of the tasks which confront telecommunication systems, calculating machines and the nervous system may form the basis for a new approach to neuro-physiology. Applications of concepts of communication to other branches of biology are less obvious, with the commonplace exception of those branches of social biology containing semantic elements such as animal "language" or phonetics. However, any geneticist, reading Wiener's *Cybernetics*[3] will, I think, find that this new way of looking at life provides him at once with certain unifying principles useful in the interpretation of many of the facts of his own science. Actually Wiener refers to genetics at various points in his book. The following record of some of one geneticist's reflections after reading Wiener's book may therefore prove stimulating to some of his colleagues; there is little doubt that they will arouse the criticism of others.

Considerations of the genes as the elements of an integrative system comparable to the nervous system are of course not entirely new, but it seems that Wiener's notions about a special class of integrative systems, namely communication systems, are new. Let us, then, first compare one of Wiener's general concepts, the *"message"* with the basic element of genetics the *gene* and let us in particular and somewhat boldly consider to what extent genes can be described as messages or as sources of messages: A gene, we may say, is a message, which can survive the death of the individual and can thus be received repeatedly by several organisms of different generations. A gene may reproduce itself faithfully and in fact we do not know of any gene which can survive without doing so; in this specific form of "racial memory" we find a curious analogy to one of the devices in electronic calculating machines, which stores sequences of signals by perpetually recreating them. Occasional faulty reproductions of such a signal (message) may be likened to mutation; signal and gene are then recreated in the new form until the next mistake is made. Re-recording of a speech or music from one record to another is yet another comparable process, which is also subject to "errors." However, usually another device is applied, namely pressing from a "negative" matrix. It is interesting in this context that a similar process has been considered by Haldane[1] as possibly responsible for gene reproduction. There is the further more specific concept that some antigens and genes may have a relationship comparable to cast and matrix.

According to Wiener, the simplest form of a message involves the possibility that it may be "yes" or "no"; the genetical analogue to this is the old *absence-presence* theory, which may not hold between the alleles in a zygote, but which applies to minute deficiencies. It is conceivable that an "all or nothing" reply by individual receptors is more commonly found in gene initiated reactions than is commonly realized. However, more complex forms of messages are probably the rule.

It would be tempting to compare the linear arrangement of genes in a chromosome to a sequence of signals on the keyboard of a calculating machine, or the spiralized body of the chromosome to the spiral of words on a phonographic record, but it should be born in mind, that the message conveyed by a gene is not numerical and that the means of delivering it are not electrical or mechanical. Speculations about the importance for gene actions of the linear

*Associate Professor of Genetics, McGill University, Montreal.

arrangements of the genes have so far not produced any convincing ideas.

Genetical messages are of a *chemical* nature and thus even greater caution against drawing excessive analogies is warranted, than in the comparison of electronic telecommunication devices and the brain where excitation is conceived in electro-chemical terms. Some usually overlooked similarities between nervous systems and genomes should be pointed out here; both are integrative (coordinating) systems (although functioning at different levels and at different times) and both are characterized by a high degree of topographic (localized) specialization. Unlike a cell in a liver lobule, which can function in the place of any other such cell, as far as bile production is concerned, a neuron in the cerebral cortex cannot function in place of a neuron in the cerebellum; lack of function in both places may have, however, similar results. Similarly, on the cytological level a cytoplasmic inclusion may not be unique, but a gene in locus *A* cannot as a rule replace the function of another gene in locus *B*—although the loss of either gene may result in similar defects. In cybernetical language we may say: neurons and genes are sending out specific messages, but liver cells and plasmons are not.

The manner in which genes act to sculpture characters has long been the subject of speculation and experiment. Many geneticists today would probably say that the gene acts through the production and release of enzymes or enzyme-like substances. These substances can be considered to be the chemical messages and they will at specific periods of the individual's development be received at specific receptive sites. These may be found in the same cell where they originated (autonomous gene action, local action); or they may be at a distance. In that case the gene may act through a hormone, the classical type of chemical telecommunication. By such processes gene-messages may thus become ultimately observable in cells of distant tissues (induced gene action, action in the distance). Gene messages may also inter-act between individuals as between fetus and mother, sometimes with disasterous results.

Broadcasting *vs* Telephoning

A difference between humoral messages and neural messages is that the former are, as Wiener points out, directed "to whom it may concern" and the latter to cells connected to the point of origin of its message by fibres. The emission of gene messages is thus more comparable to broadcasting, and the transmission in the nervous system to wired telecommunication. However, there is the difference that homologous genes in many cells can function as "broadcasting stations." If we multiply the number of genes (loci) per cell (estimated for man to vary between 5,000 and 10,000) with the cell number in man, the product number is quite comparable with the estimated billions of neurons found in the brain.

An important similarity between a message and a gene is, that they can both be regarded as "Gestalten," i.e. as meaningful structures, and that their loss can be regarded as a loss of "negative entropy." In telecommunication as well as in genetics, consideration of energy is thus of much less importance than consideration of an entity comparable to entropy. This is not the case if we consider power engineering or the function of such organs as the liver or the muscle.

It could be objected, that the concept of gene action as a sort of enzyme action has proved so valuable, that one should not easily discard it. In fact there is no need to do so; the message concept of gene action is complementary to the enzyme concept; it indicates the specific task or what is sometimes called the primary action, a gene performs in the development, maintenance, regeneration or function of an organism.

The message of a gene may not reach its destination during the life of every organism carrying the gene; the individual may die before a receptive situation

occurs, e.g. a man carrying a gene for Huntington's Chorea which has a late manifestation at say age 40, may perish in a street accident at 20. A plant genetically susceptible to infection with rust, may never be exposed to rust infection. The message may not be received for internal reasons; a woman carrying the gene for premature baldness will not get bald before menopause because she has the female hormonal constitution (sex-limited manifestation). The message may finally be crowded out by a similar but contradictary (allelic) message in the case of a recessive. But the message can still be handed on to the next or a later generation regardless of whether it was effective in this generation or not.

In the same way as a ship or a factory can only be built and run by efficient methods of direction, an organism can only be kept alive by effective communication systems. During organogenesis and even earlier, organizers and similar local structures assume the role of centers of local organization, though even then some also act at a distance. However, there is little doubt that special messages, reaching specific tissues at specific times, are originating from genes whether in nearby or distant cells, though they may be modified on their passage to the site of action.

The "Feed-Back" and Memory

Messages also reach the genetical system from the periphery; Wiener's "feed-back" is a device comparable to an animal's sense organs which gathers information from the periphery to guide the action of such self-steering machinery, as guns or torpedoes. The "feed-back" is paralleled on the level of population genetics by the process of selection which provides the regulating (eliminating etc.) peripheral messages, which decide the future of genes, individuals and populations. Messages are thus concerned in the maintenance of genetical stability (homoeostasis). Phenotypical constancy may be achieved by a change of reception of allelic messages (change of dominance).

The permanency of memory as popularly understood has been often stressed —"the elephant never forgets"—but it is certainly surpassed by the permanency of the genes, which carry their messages through the generations. This in turn implies certain restrictions on the content of those messages, which it might be interesting to investigate. Memory of a particular event can be helpful to an individual only if situations pertinent to this memory recur; it would be useless to learn things, which will never become applicable in any way. Similarly the message of a gene will, one might assume, only be kept through the ages if it fills a role in the development of successive generations. A primary gene action will thus presumably refer to a developmental situation, recurring at least once in every generation. This may throw some light on what sort of messages (primary gene actions) we might expect and at what level they would be received. The most constant elements in a single gene's environment are probably all the other genes and consequently its message will be most easily applied to situations, predominately controlled by those other genes, i.e. during development.

The next most constant elements are those stereotyped ecological factors, which constitute within a certain range the "normal" environment for the species. It is well known that many environmental factors, e.g. temperature or nutrition, may suppress the manifestation of genes and thus reduce the effectiveness of their messages. Within reasonable limits constancy of conditions during comparable phases in the life cycles of individuals in successive generations would appear necessary to make a gene message useful. This does not rule out very special messages, such as the genetically fixed responses of parasites to the presence of their hosts; it does rule out genetical fixation of messages relevant to conditions, which are not regularly experienced by the

members of a species, and it permits the possibility of any speedy adaptation to new conditions. If we consider a gene as a message, and are rash enough to argue from analogy, Lamarckism would appear rather more absurd than otherwise.* The rapidly shifting material and social conditions of man in particular would leave almost no space in the chromosomes and certainly no time for the incorporation into his genome of new gene messages, like Semon's[2] "mnems."

Three Levels of Control

It looks as if man has had his genetical adaptation before modern civilization started (pre-adaptation) and that it consists in the development by the control of many genes of that most adaptable communication system, the brain.† By reason of this system man thus does not master problems new to the species by special gene mutation (i.e. new messages on the nuclear level) but by using this new, bigger and superior, integrative machine. The efficiency of this machine, which works on the cellular and organ level is gauged by its adaptability and stability; hence the increasing importance for human survival of his intellectual and emotional faculties.

The great efficiency of his brain has enabled man not only to develop the old and traditional ways of communication, like gesticulation, language, and writing but also in more recent times modern telecommunication. In a social species like ours we thus find in the main, three cybernetical or integrative systems at work: (1) the genetic system, which, working on a nuclear level controls cell function, (2) the nervous system, working on a cellular (neural) level which coordinates organs and (3) those inventions, which enable the members of a society to exchange what is commonly understood as messages. At present (2) and (3) are much nearer the focus of general interest, than (1). Nevertheless, no organism, solitary or social, is conceivable, which has not grown under the control of a well integrated communication system, the elements of which are the genes.

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*It is rarely realized, that individual adaptations are processes, the physics and chemistry of which are probably less understood, than are the mechanics of variability and selection which we assume to produce species adaptation. Here it must suffice to indicate that it is usually the adaptability (the range of possible adaptation) of an organism which is genetically controlled. The appearance of the individuals of many plant species is different at sea level and at high altitude, but this habitus is largely under environmental control; similarly the weight of an animal's heart and muscles depends on the work it has done. We do not know what messages make a plant grow taller or a heart stronger.

†Doubling of the number of neurons by one more cell division would, as has been pointed out, enormously increase the scope for neural action.

THE INHERITANCE OF ALKAPTONURIA

In a Large American Family

W. KNOWLTON HALL, KATRINE RAWLS HAWKINS, AND GEORGE P. CHILD*

ALKAPTONURIA is a rare metabolic disease in which an inborn error of metabolism of the amino acids, phenylalanine and tyrosine, results in the excretion of homogentisic acid (2, 5-dihydroxyphenyl acetic acid) in the urine. Urine containing homogentisic acid and in contact with air darkens slowly on standing, or rapidly if alkali is added. Homogentisic acid reduces Benedict's or Fehling's solutions and gives a transitory blue color with ferric chloride solution.

Boedeker† in 1861 reported finding a reducing substance in urine which he named "alkapton" because of its behavior with alkali. Wolkow and Baumann[13] in 1891 determined that "alkapton" was homogentisic acid.

A normal individual is able to metabolize administered homogentisic acid, while in alkaptonuria, the acid when administered is excreted unchanged.[6] In alkaptonuria, ingested phenylalanine and tyrosine are excreted nearly quantitatively as homogentisic acid.[6, 11, 9]

After administration of large amounts of tyrosine to man,[6] the mouse,[8] or rat,[3, 2] homogentisic acid may be found in the urine. In the rat,[10, 4, 5] or mouse,[8] after the administration of phenylalanine or in the scorbutic guinea pig[12] after feeding tyrosine, some homogentisic acid may appear in the urine.

Alkaptonuria in the Literature

Scribonius[6] in 1584 was the first to describe the condition now known as alkaptonuria and since then sporadic cases have been reported totalling over 200 in the world literature. Abbott[1] in 1941, on reporting two cases of alkaptonuria in American negroes, stated that to that time only 21 cases had been reported in the United States.

The most common complications of alkaptonuria are arthritis and ochronosis. In ochronosis, with age, there is a progressive darkening of cartilage, most noticeable in the ears and nose. Sometimes there is a darkening of the fibrous tissue of the skin in some areas, and darkened areas may also be observed in the sclera. Ochronosis was first described by Virchov[6] in 1866, and in 1902 Albrecht suggested that alkaptonuria might be the cause. Osler and a number of others have since reported cases with ochronosis.

Bateson[6] in 1902 concluded that alkaptonuria was inherited as a recessive character. Since then, many family histories have been reported which confirm this suggestion and some which do not. Thirty years later Hogben, Worrall and Zieve[7] analyzed the mode of inheritance in 45 families reported in the literature and found that the character was dominant in three families, recessive in 41 and questionable in one.

The sex distribution reported is variable although in the cases reported in the literature males predominate.

Most of the reported cases have been in white people although Abbott,[1] as mentioned above, discovered two cases in a Virginia negro family.

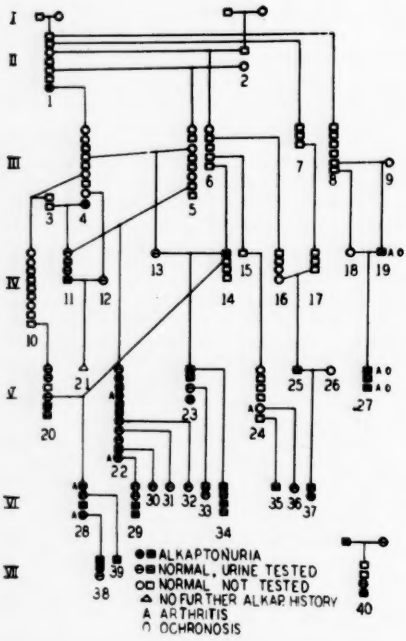
A New Family with Alkaptonuria

The kindred reported in the present paper consists of white people of German, English and Dutch, Scotch or Irish extraction who are descendents of the original settlers of the county in which they live. Two of these early settlers were living on land grants at the time the county was established in 1793. The character was presumably brought in by the English branch of the family. A number of the family have migrated and are lost to the kindred. Some who have moved from the area to known

*Department of Biochemistry, University of Georgia School of Medicine, Augusta, Ga., Sylvania, Ga., and the Department of Physiology and Pharmacology, Albany Medical College, Albany, N. Y.

This study was possible because of the helpful cooperation of the people constituting the kindred. The investigation was supported in part by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

†A good review of the older literature will be found in Garrod's book.[6]



SIX GENERATIONS OF ALKAPTONURIA

Figure 8

A new family pedigree of Alkaptonuria in which the inheritance is typically recessive. The "dark urine disease" is also responsible in some cases for arthritis ,and the deposition of pigment in the cartilage, especially that of the ears and nose.

localities, as well as about half of the kindred still resident in the county, have not been investigated. The investigation of one portion of the family was facilitated by their custom of holding monthly family reunions. The family relationships in the kindred are shown in Figure 8.

In general the individuals of the kindred are dark-skinned and most have medium dark to dark hair. The siblings, No. 22, are unusually dark complexioned and have a scattering of moles. Despite the considerable amount of inbreeding they are average or above in intelligence and physical development. The siblings, No. 27, for example, are well established business people and prominent in the community.

The sex distribution among the alkaptonurics in the kindred is ten females to five males among a population having two males to one female. There is another alkaptonuric male in the isolated line. Since the number of alkaptonurics is small, probably no great significance should be attributed to this distribution. However, this ratio of two female alkaptonurics to one male in our kindred might be considered as evidence supporting the suggestion made by Hogben, Worrall and Zieve[7] that the ratio of 100 males to 46 females which they found in their review of the older literature might reflect the fact that males are less disposed to reticence concerning micturition than are females.

All but one of the alkaptonurics were known to possess the character at birth or soon thereafter since the urine discolored the clothing and bedding.

Figure 8 shows the considerable amount of inbreeding which was responsible for the character manifesting itself in so many individuals. If the gene is recessive, it is necessary to assume that the parents of No. 1 were heterozygous and that No. 26 and No. 9 were also heterozygous. From No. 33 the information has been obtained that No. 26 was a relative of No. 25. The siblings, No. 27, do not know whether their grandmother, No. 9, was a relative of No. 8. The kindred, otherwise, supports the recessive hypothesis.

The geneology of the isolated alkaptonuric in No. 40 could be traced four generations and was found to be unrelated to the larger kindred. This family, however, has never lived farther than 50 to 100 miles from the large group and, since we are dealing with small populations, it is likely that these families are related to one another. This view is supported by evidence from metabolic studies which will be presented in a later paper. The parents of No. 40, furthermore, claim to be completely unrelated other than by marriage. Their

first two children, incidentally, were amyelencephalics and died at birth.

Although arthritis and ochronosis are often associated with alkaptonuria only No. 19 and No. 27 showed this triad. The ochronosis found here was quite extreme. Arthritis was found in No. 22 and No. 28 and in a non-alcaptonuric, No. 24.

Approximately 300 individuals of this kindred have been examined for alkaptonuria. It is probable that there are additional cases of alkaptonuria among the 300 or more individuals of the kindred not yet investigated.

Reports of clinical examinations and metabolic studies made on these alkaptonurics will be published elsewhere.

Summary and Conclusions

Sixteen cases of alkaptonuria have been found in a locality in Georgia. Fifteen of these were found among 300 people investigated from a large kindred which has been traced for seven generations. The other case was found in an apparently unrelated line. The character seems to be a simple recessive, and the sex ratio among the 15 alkaptonurics in the kindred was ten females to five males among a population whose ratio was two males to one female. Arthritis and ochronosis were associated with the alkaptonuria in three cases and arthritis alone in two.

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◆

The Last One Percent

It is very generally overlooked that the period during which food production has been carried on is but 1 percent of the duration of the human story, and that the period since the idea of regular cultivation (at any rate of cereals) began to spread from its primary home in the South-West of Asia and the North-East of Africa is much less still. This means that for over 99 percent of its period on earth mankind has lived in small groups bound together by many ties, even if they fluctuated to some extent. Further, even after the spread of cereal cultivation, the social group long remained small and the mentality accompanying traditional sociality was not forced to change very radically. Here and there large agglomerates appeared—Babylon, Athens, Rome, and so on—and began the atomization process, the individual becoming liable to be a lonely unit in a crowd, a condition not at all in keeping with the mentality engendered by his history of 600,000 years. Prodigious technical experiments and prodigious flights of thought have been crowded into a mere 4,000 years or less, and this crowding has become intensified a hundredfold since power-machinery became available and gathered men into industrial agglomerates that are called modern cities. We are witnessing in the twentieth century the result of this violent dislocation of traditional social psychology, a dislocation long inadequately realized because men dealt with a six-thousand-year-period since the creation of the world. The nineteenth-century abstraction called economic man, the religious abstraction called fallen man, and many other ideas still in current use are very much out of perspective, as is the notion that one can remould man quickly by changing environment.— J. H. Fleure, *Eugenics Review*, October, 1949.

A CYTOLOGICAL BASIS FOR STERILITY IN TOMATO HYBRIDS

Evidence for an Inversion in one Chromosome of the F_1 between *Lycopersicon Esculentum var. Pearson* and *L. Peruvianum* P. I. 126946

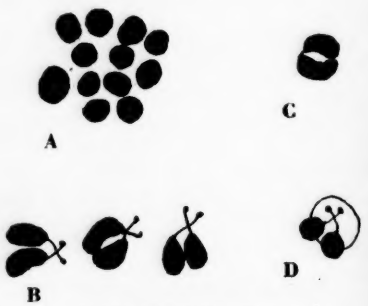
MARGARET MANN LESLEY

THERE have been many attempts to cross *L. peruvianum* with *L. esculentum* since it has been found that *peruvianum* is resistant to certain diseases that afflict cultivated tomatoes. The results have mostly been disappointing. Although the pollen of *peruvianum* germinates on the tomato stigma and fertilization occurs, the embryos rarely complete their development so that mature seeds are rarely found in the ripe fruit.*

Smith[12] succeeded in growing an F_1 plant of Michigan Forcing × *L. peruvianum* P. I. 128657† by using embryo culture. By similar methods J. W. Lesley obtained an F_1 hybrid of Pearson × *L. peruvianum* P. I. 126946. The pollen parent of this cross resembled the type species of *peruvianum* as described by Muller[10] and was similar to the subspecies *commutatum* of Luckwill[8]. It bloomed and set fruit freely at Riverside in summer. Pearson is a very fruitful variety. The F_1 is intermediate in appearance. It is very large and vigorous and flowers freely, but thus far it has failed to set fruit either with its own or with *esculentum* pollen. Its pollen has produced fruits but no mature seeds when used on *esculentum*.

Meiotic Behavior

In the common tomato, the chromosomes differ in size by such small increments that except for the nucleolar pair one cannot certainly identify any of them in meiosis. In *L. peruvianum* P. I. 126946 and in a variety described by J. W. Lesley[5] one non-nucleolar pair with trabants is distinctly larger than any other. The large pair has not been found in *L. peruvianum dentatum*. Meiosis is normal in P. I. 126946 and in Pearson.



SIZE DIFFERENCES

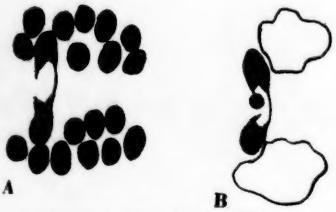
Figure 9

A—First metaphase showing complete pairing and one large pair. *B*—The largest pair at diakinesis. *C*—The unequal-looking pair at diakinesis. *D*—The nucleolar pair at diakinesis.

Pairing of chromosomes in the pollen mother cells of the F_1 is normal at diakinesis and first metaphase (Figure 9). In early first anaphase the largest pair is held together by a bridge (Figure 10) in about 20 per cent of the observed cases (23 with a bridge, 88 without). The members of this pair often lag slightly at first anaphase, but are usually included in the set by late anaphase or telophase. Lagging whole chromosomes are exceedingly rare. One small fragment is frequently seen in late anaphase and several are sometimes found (Figure 11). The fragments are usually surrounded by a clear area indicating that they are disintegrating. They are stained very slightly in carmine or orcein but are distinctly stained with gentian violet. A few cells show bridge remnants and abnormal spindles at late anaphase or telophase. The cytoplasm of these cells is more deeply stained than that of normal cells. They are probably abortive (Figure 12). Some of them appear to have several bridge remnants.

*J. W. Lesley,[5] Smith,[12] Cooper and Brink,[3] and Bohn[2] found no mature seeds; Wright and Lincoln,[13] Alexander *et al.*,[1] Yeager and Purinton,[14] and Porte and Walker[11] found a few mature seeds. Holmes[4] and Lesley and Lesley[6] obtained mature seeds from crossing *esculentum* with *L. peruvianum dentatum* (*L. chilense* Dun).

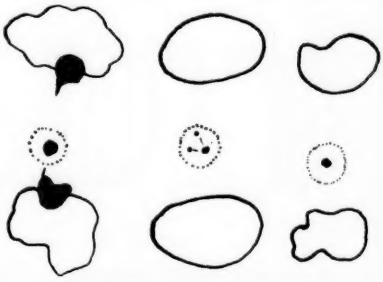
†Division of Plant Exploration and Introduction, U.S. Department of Agriculture Number 128657.



BRIDGES AND FRAGMENTS

Figure 10

A—A typical bridge involving the largest pair at first anaphase. Some chromosomes are omitted. *B*—A slightly later stage showing lagging of the largest pair and an unusually large fragment.



FRAGMENTS FADE OUT

Figure 11

First telophase showing degenerating fragments.

At second anaphase the larger pair also often separate more slowly than the others and occasional fragments occur (Figure 13). Most tetrads look normal and the young pollen is approximately even, but about half the pollen grains are empty at anthesis. The other grains vary greatly in size and ability to stain with aceto-carmine. Many of them are clearly abnormal so that not more than a third of the pollen would be functional.

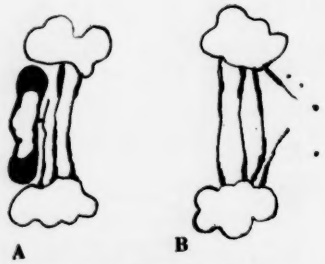
The race of *L. peruvianum dentatum* (*L. chilense*) grown at Riverside was obtained by Holmes from a twelve-year-old herbarium specimen. The plants are very different from the other races of *peruvianum* in that they grow very poorly, produce very few flowers and have few pollen mother cells. Only one plant fruited. It had normal chromosomes which paired, but from one to three homologues were commonly less closely paired than the others and all of them tended to disjoin in hot weather. Several hybrids were obtained with *esculentum* and with an *esculentum* × *pimpinillifolium* hybrid. The diploid F_1 is a large plant which shows dominance of *dentatum*. It is nearly self-sterile, but yielded some viable seed when backcrossed to *esculentum*.[6] About two thirds of the mature pollen in the F_1 are clearly abnormal. In most smears there are a few germinating grains.

Discussion

All species of *Lycopersicon* which have been examined have twelve pairs of chromosomes and twelve pairs have been found in all F_1 species crosses thus far described. In general, crossing is easiest within the sub-genera[9]. *L. esculentum* × *peruvianum* is one of the most difficult crosses. Smith found that although fertilization occurs, the embryos grow at very different rates. The endosperm becomes insufficient after about thirty-five days. If cultured, some of the larger embryos develop into large and normal F_1 plants. They are self-sterile. Pollen of the F_1 has produced a few normal seeds with *peruvianum* but has failed on tomato. Smith suggests that embryo culture will have to be used here also.

McArthur and Chiasson[9] conclude that there is no evidence that major structural rearrangements in chromosomes are barriers to crossing or causes of the partial sterility of the diploid interspecific hybrids in *Lycopersicon*. They consider that "genic, perhaps multiple factor differences between the species seem the most likely causes of such hybrid sterility as exists." They conclude that "if structural hybridity of some degree exists . . . it would be of the cryptic type due to minute chromosome rearrangements." The bridges found in F_1 *esculentum* × *peruvianum* are probably due to one or more small inversions since the chromosomes pair regularly and the fragments are usually small. The presence of an extra fragment or the loss of one might cause some of the pollen abortion, but one would not expect it to cause as much as two-thirds. It looks as if certain chromosomes of *peruvianum* cannot wholly replace their *esculentum* homologues. This is the more likely since the chromosome sets of the two parents differ and one chromosome pair in the F_1 appears to be heteromorphic.

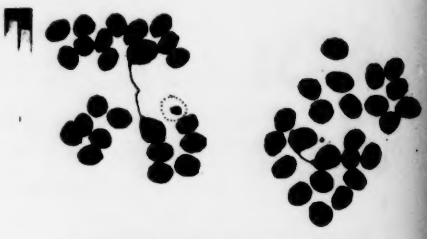
Although the wild varieties of *esculentum* and *peruvianum* are both native to



MEIOTIC DISORGANIZATION

Figure 12

A—Degenerate-looking cell with largest pair still undivided at first telophase and many strands connecting the two nuclei. *B*—A similar cell with several small fragments and a broken strand.



STRAND ACROSS THE EQUATOR

Figure 13

Two second anaphases from the same cell showing the largest pair connected by a strand after all other chromosomes have divided. There is a small fragment in the left hand figure.

western South America, they appear to have very different day length requirements. Luckwill[8] found that *peruvianum* requires shorter days than *esculentum* in order to flower.

The factors which keep the two species apart include:

1. Differences in response to environmental conditions.
2. Difficulty in crossing.
3. Rare maturing of F_1 embryos.
4. Two-thirds pollen abortion in the F_1.
5. Failure to backcross to tomato.

Summary and Conclusion

1. The embryo from an immature seed from the cross *L. esculentum* × *L. peruvianum* P. I. 126946 was cultured and grew into a large and vigorous but very unfruitful F_1.

2. At diakinesis and metaphase I all chromosomes of this F_1 were neatly paired and division occurred normally except for bridge formation.

3. About 20 percent of the pollen mother cells of the F_1 showed a bridge involving the largest pair of chromosomes at early anaphase I.

4. At late anaphase and telophase I small chromosome fragments were found on the spindle.

5. From the prevalence of bridge and fragment formation it is concluded that a section of the largest chromosome of one parent is inverted relatively to that of the other. Crossing over in this section would cause fragment formation.

6. One other pair of chromosomes appears to be unequal.

7. At least half the pollen is empty at anthesis and much more is clearly abnormal. Some of the pollen sterility of the F_1 is probably caused by small deficiencies or duplications, due to loss or addition of small fragments. It is also suggested that certain chromosomes of *peruvianum* cannot wholly replace their *esculentum* homologues.

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